ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

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To Induce, or Not to Induce, that is the (Still Unanswered) Question

Robert J. Soiffer

A 41 year old man presents to you with pancytopenia. He is asymptomatic except for mild fatigue. Liver, pulmonary, and kidney function are normal. Bone marrow biopsy is normocellular with multilineage dysplasia. Myeloblasts represent 15% of the marrow cellularity. There are no circulating peripheral blasts. Chromosome analysis reveals monosomy 7 in 13 of 20 metaphases. The patient's brother is healthy and HLA-identical. Based on the patient's diagnosis of myelodysplastic syndrome, high international prognostic scoring system, lack of comorbidities, and available HLA-identical sibling donor, you recommend allogeneic hematopoietic cell transplantation (HCT) [1].

Your fellow asks you, "Do you think we should treat the patient first in order to decrease the number of marrow blasts before transplantation? Will that lead to lower relapse rates and superior long term survival? Should we use a hypomethylating agent or do you think full leukemia induction with cytosine arabinoside and anthracycline is best?" You pause, stroke your chin, and prepare to educate your knowledge hungry fellow. But the best you can do is reply, "I don't know."

Although allogeneic HCT has been performed for myelodysplasia for over 25 years, there remains no clear consensus on the advisability of cytoreductive therapy before transplantation. Unfortunately, there are no randomized trials to help guide practitioners and retrospective studies are generally subject to selection bias. Nonetheless, Scott et al. [2] reported in *Biology of Blood and Marrow Transplantation* in 2005 a series of 125 patients with advanced myelodysplastic syndrome (MDS) treated in Seattle with myeloablative transplantation. In that retrospective series, 33 patients received induction chemotherapy whereas 92 patients were taken directly to transplantation. No significant difference in relapse-free or overall survival was noted in patients who had received pretransplant chemotherapy compared with those who were chemotherapy naïve. This of course does not even account for those patients with advanced MDS who received induction chemotherapy and never received a transplantation either because of morbidity from treatment or lack of response to the induction chemotherapy. Nakia et al. [3] reported a similar experience from Japan, again in ablative transplantation recipients. The impact of induction chemotherapy may be different in patients receiving nonmyeloablative conditioning as the experience reported by Warlick et al. [4] in Minnesota suggested a trend for better outcome in nonmyeloablative recipients who had received pretransplant treatment.

In this issue of the *Biology of Blood and Marrow Transplantation*, Saure et al. [5] present a novel strategy for patients with advanced MDS. They treated 30 patients with fludarabine, amsacrine, and cytosine arabinoside followed 2 to 3 days later by high dose melphalan-based conditioning and allogeneic hematopoietic stem cell infusion. Thus, induction chemotherapy was actually combined with allogeneic HCT rather than delivered as a 2-step process. They report an encouraging 63% 2-year disease-free survival estimate.

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Financial disclosure: See Acknowledgments on page 333.
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Received January 4, 2012; accepted January 6, 2012

1083-8791/$36.00
doi:10.1016/j.bbmt.2012.01.002

Caution, however, must be exercised in interpreting these results. The patients included in this series were heterogeneous with a third having refractory cytopenia with multilineage dysplasia and refractory anemia with excess blasts-1 and 40% reported as having "good" cytogenetics. None had received prior hypomethylating agents which may skew the population. Relapses were still observed beyond 2 years so durability of the 2-year survival outcomes is uncertain. No data are presented which correlate percentage of marrow blasts at transplantation with risk of posttransplantation relapse. Nonrelapse mortality was high (30%) and correlated with intensity of transplant conditioning, raising questions about applicability of this strategy to older patients, such as those aged 60 and higher. It is particularly important to focus on this older population as they represent an increasing percentage of patients for which HCT is performed for MDS and they generally receive reduced intensity conditioning. Combining induction chemotherapy with aggressive transplantation conditioning may not be tolerable for this cohort.

Although we can now add this report by Saure et al. [5] to the literature we give to our fellows, we still are not really any closer to determining the best course of action for our patient presented above. It will take a large committed multicenter effort to test this strategy in a prospective randomized trial. Given the increasing frequency of MDS as a transplant indication, it is a question we as a community should answer.

ACKNOWLEDGMENTS

Financial disclosure: The author has no relevant conflict of interest to disclose.

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